

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Tapas Mukhopadhyay, *et al.*

Group Art Unit: 1642

Serial No.: 10/043,877

Examiner: B. J. Fetterolf

Filed: January 9, 2002

Atty. Dkt. No.: INRP:095US

For: ANTIHELMINTHIC DRUGS AS A
TREATMENT FOR
HYPERPROLIFERATIVE DISEASES

**SECOND DECLARATION OF TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER
MHASHILKAR, AND JACK A. ROTH UNDER 37 C.F.R. §1.131**

We, Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, hereby declare as follows:

1. We are the joint inventors of the subject matter claimed in the above-referenced patent application, U.S.S.N. 10/043,887, filed January 9, 2002.
2. We are submitting this declaration to set forth facts demonstrating that we both conceived the idea of the invention as reflected in the claims of the above-referenced patent application and determined that it functioned, prior to March 9, 1999.
3. Submitted as Exhibit 1 to this declaration is a copy of a FACS assay showing our experiments and results, entitled figures "1A" and "1B" which was prepared prior to March 9, 1999.

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Tapas Mukhopadhyay

4. Submitted as Exhibit 2 to this declaration is a copy of our experiments and results in a study of the treatment of p53 wild type lung cancer cells with fenbendazole, which took place prior to March 9, 1999.

5. Exhibit 1 shows the results of our cell cycle analysis involving A549 (p53 wild type) non-small cell lung cancer (NSCLC) cells that have been treated with fenbendazole. The results show that the untreated A549 cells (A549C), have a standard profile of cells in various phases of the cell cycle, G1/S/G2, indicating a dominant G1 population. In contrast, the fenbendazole treated cells (A549 7EN) show a depression of both G2 and S phases and a G1 block. Furthermore, the fenbendazole treated cells show a distinct sub-G0-G1 population indicative of apoptotic cells. We generated the results of this cell cycle analysis prior to March 9, 1999.

6. Exhibit 2 shows the results of our study of the treatment of p53 wild type lung cancer with fenbendazole. We determined that treatment of p53 wild type lung cancer cells with fenbendazole inhibits growth. The study evaluated growth of lung cancer cells or normal lung epithelium (NHBE) after treatment with fenbendazole (labeled FEN in the figure) and other agents. Both H1299 and H322 are p53 deficient NSCLC cells and show modest growth inhibition by fenbendazole after 5-7 days. In contrast, the p53 wild type cells A549 and H460 show dramatic inhibition of cell growth by fenbendazole that is evident by day 1-3 and 50-80% growth inhibition by day 5-7 of treatment. The control normal cells, NHBE do not show growth inhibition by fenbendazole. We generated the results of this study prior to March 9, 1999.

7. All work disclosed in the invention disclosure form was conducted in the United States of America.

Texas Instruments

8. Therefore, the invention as reflected in the claims of the above-referenced patent application was reduced to practice prior to March 9, 1999.

9. We hereby declare that all statements made by our own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

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Tapas Mukhopadhyay

Date

Sunil Chada

Date

Abner Mhashilkar

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Jack A. Roth

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Tapas Mukhopadhyay

Date

Sunil Chada

Date

08/10/05

Abhishek Mhashilkar

Date

Jack A. Roth

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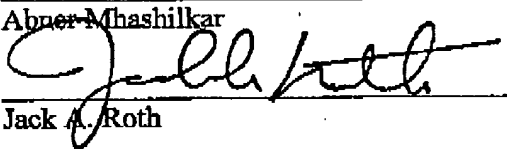
Sunil Chada

Date

Abner Mhashilkar

8-15-05

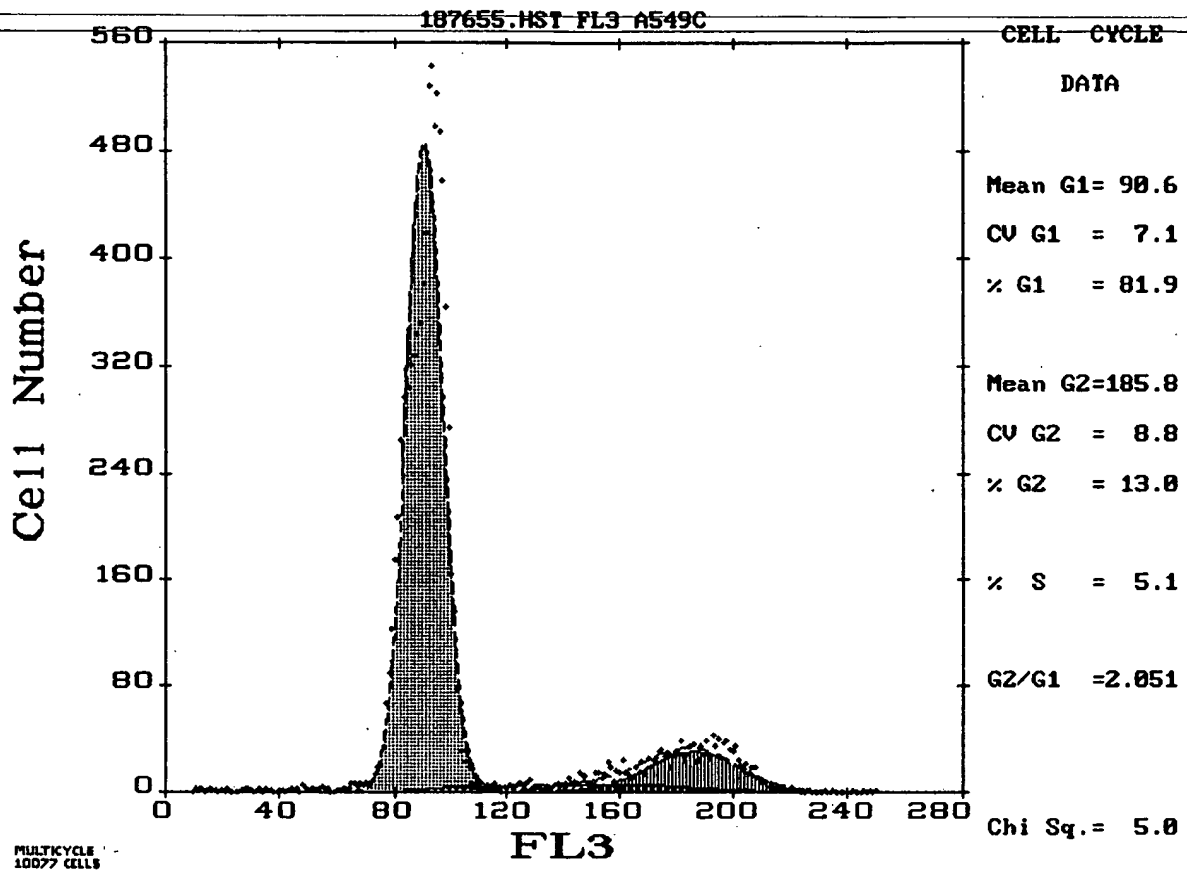
Date



Jack A. Roth

Exhibit 1

① A



① 3

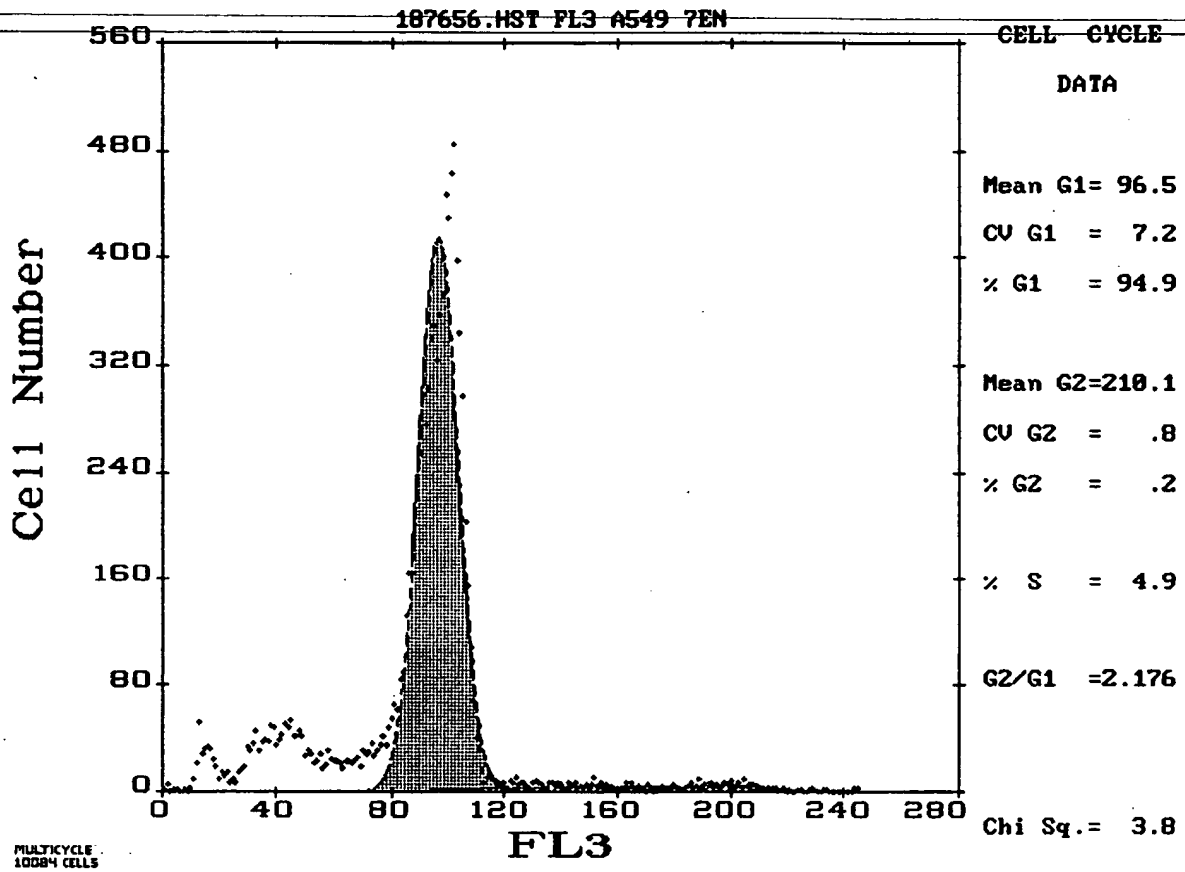
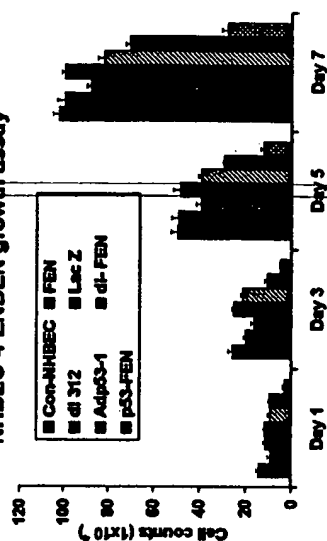
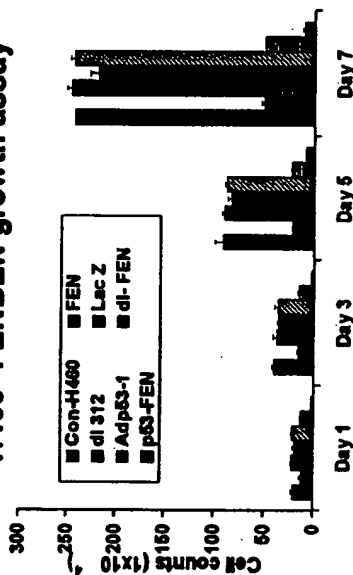
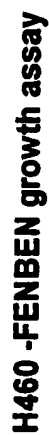
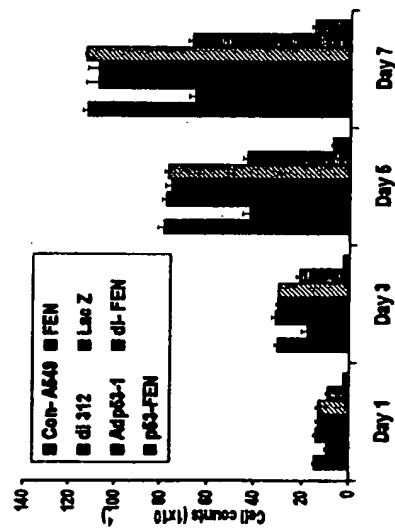
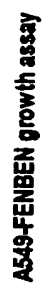
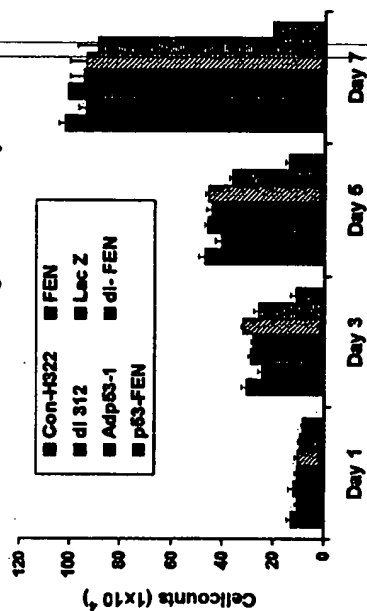
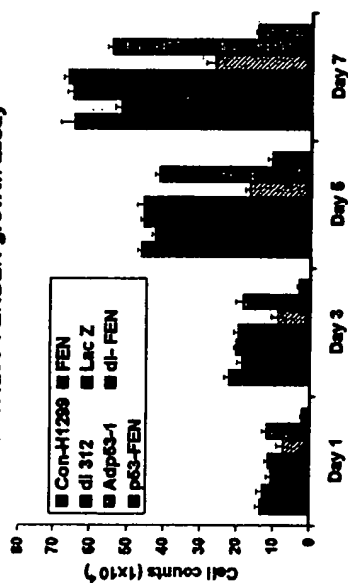
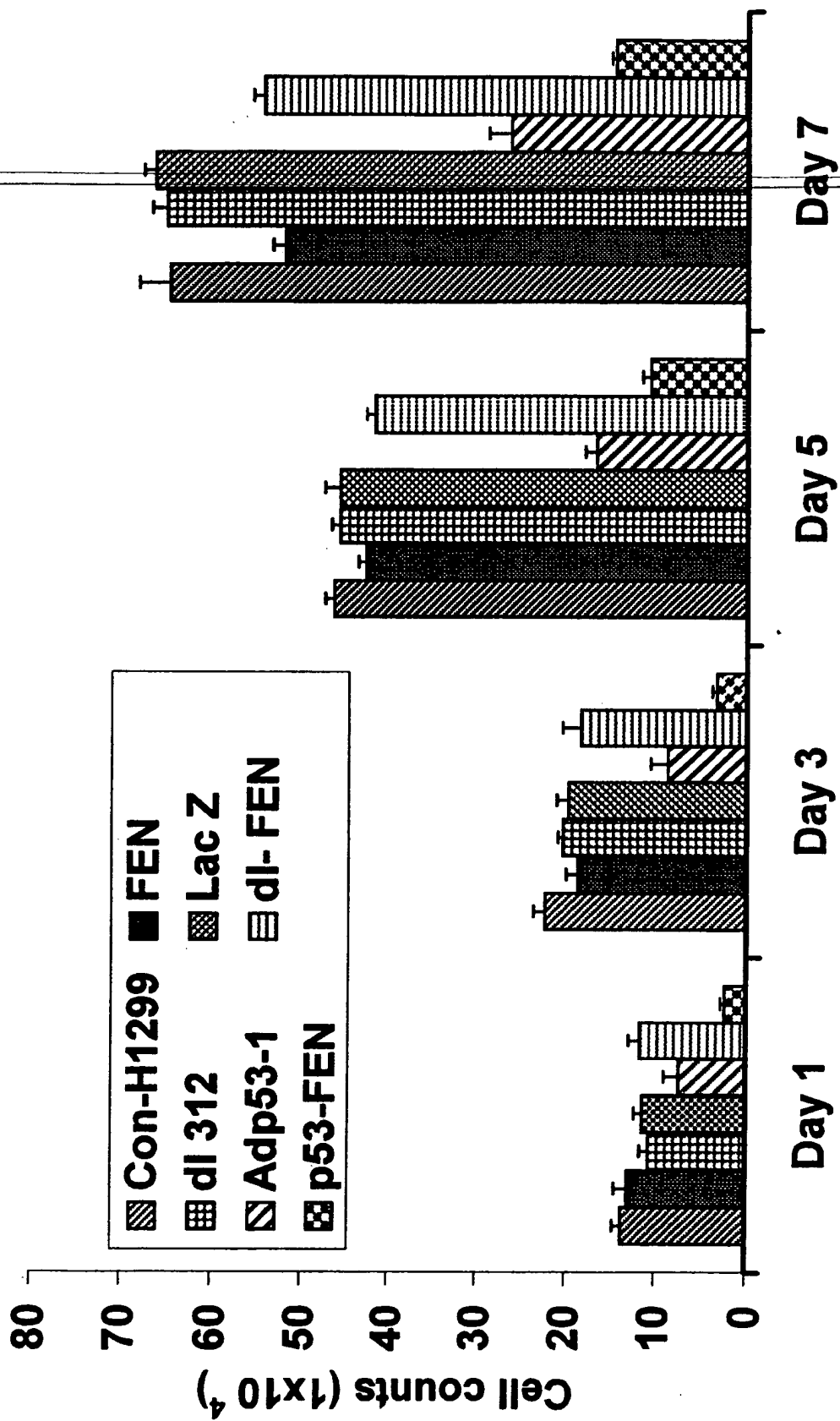


Exhibit 2

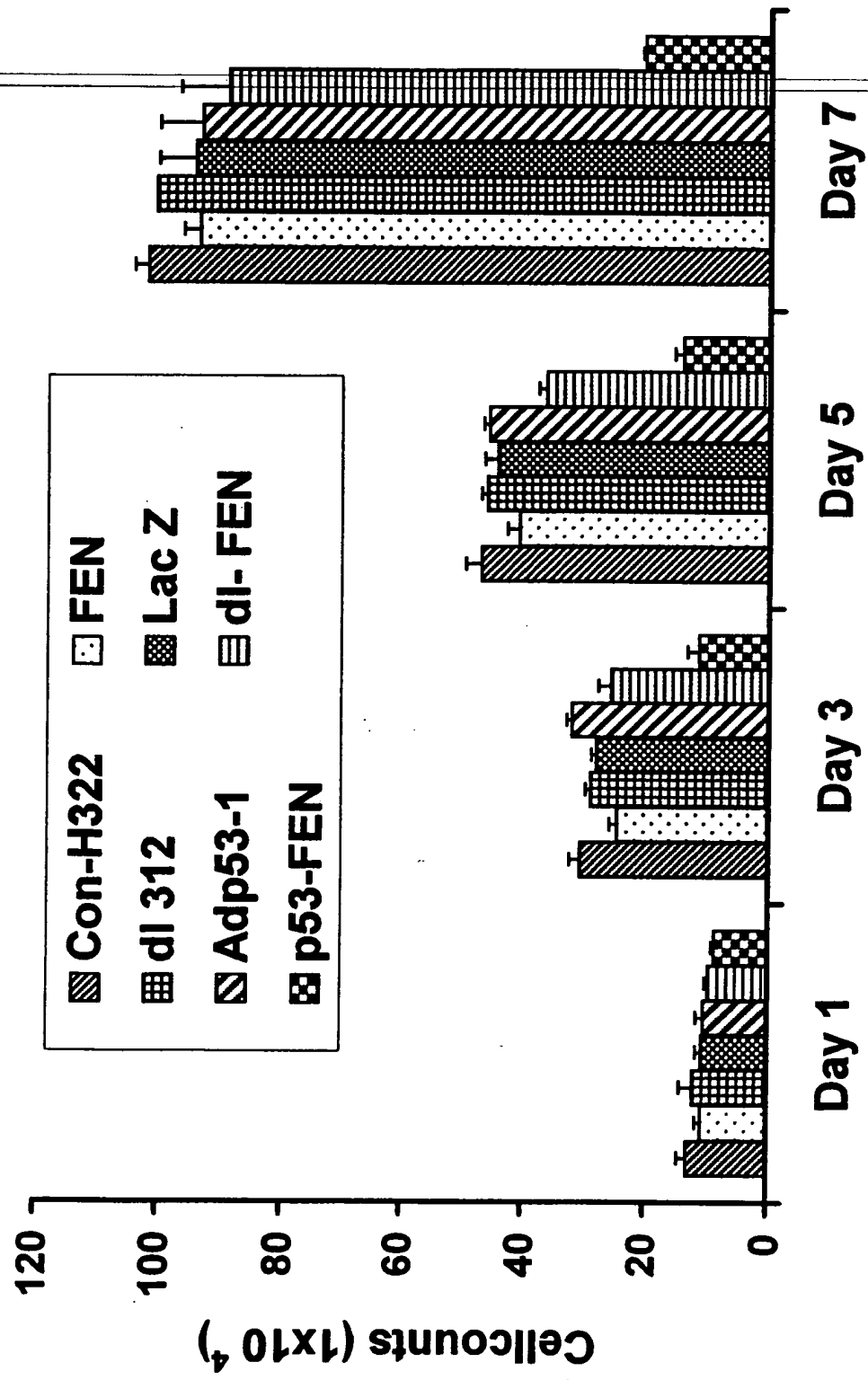


H1299-FENBEN growth assay

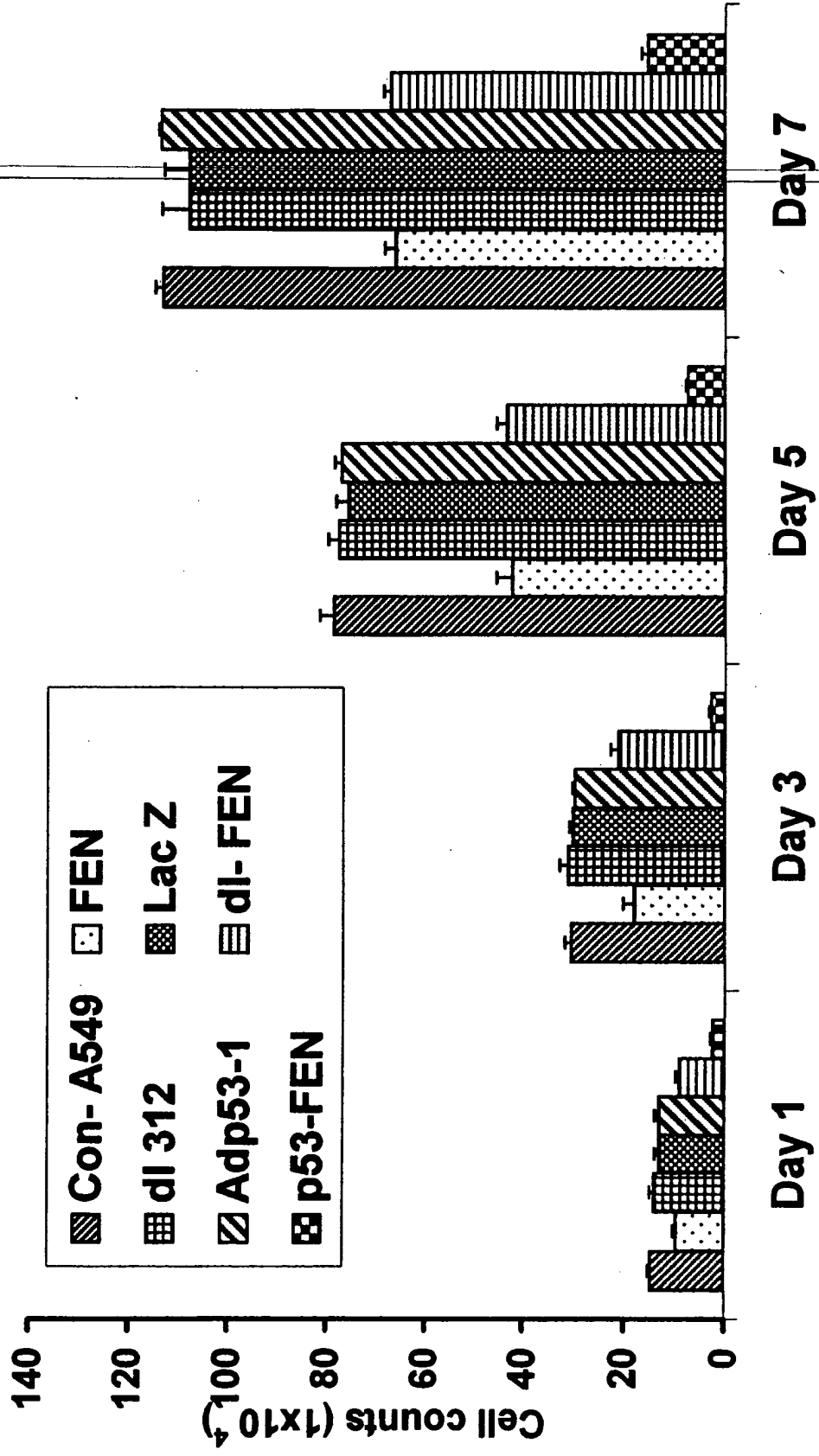


Cell counts (x10⁴)

Group	Day 1	Day 3	Day 5	Day 7
Con-H322	~10	~28	~45	~105
dl 312	~12	~30	~48	~108
Adp53-1	~10	~28	~45	~105
p53-FEN	~12	~30	~48	~108
FEN	~10	~28	~45	~105
Lac Z	~12	~30	~48	~108
dl-FEN	~10	~28	~45	~105

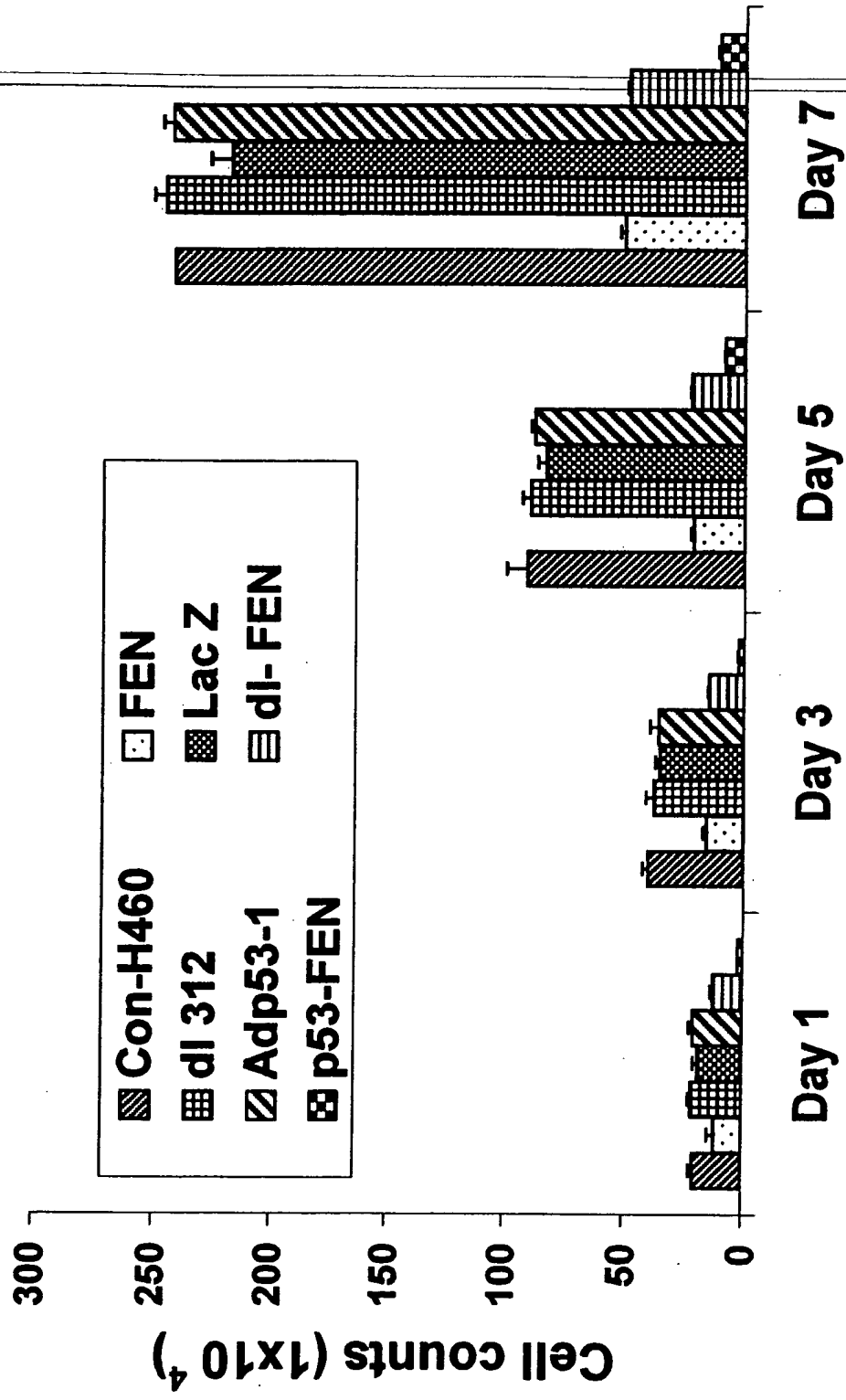


A549-FENBEN growth assay

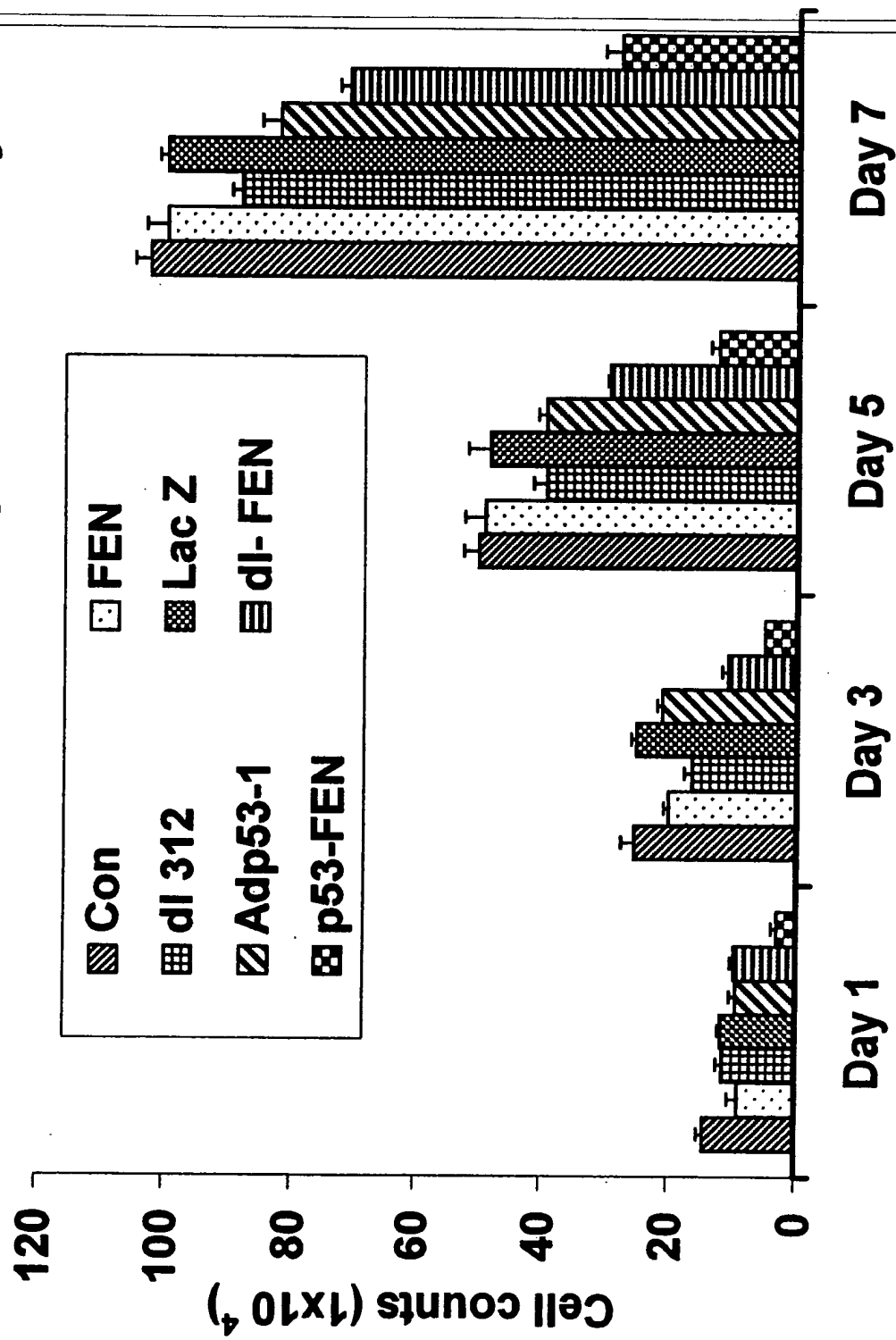


Bar chart showing cell counts (x10⁴) for various cell lines (Con-H460, dl 312, Adp53-1, p53-FEN, FEN, Lac Z, dl-FEN) at Day 1, Day 3, Day 5, and Day 7. Cell counts generally increase over time for all groups, with Con-H460 and dl 312 showing the highest counts.

Cell Line	Day 1	Day 3	Day 5	Day 7
Con-H460	~20	~40	~110	~250
dl 312	~20	~40	~110	~240
Adp53-1	~20	~40	~110	~230
p53-FEN	~20	~40	~110	~220
FEN	~10	~20	~10	~10
Lac Z	~10	~20	~10	~10
dl-FEN	~10	~20	~10	~10



HNBEC -FENBEN growth assay



NHBE

7-en 105mg
 dld312 mol=1
 V3 mol=1

	Day 1		Day 3		Day 5		Day 7							
Control	x2	30	15	x2	50	25	x3	70	53	x5	79	44		
	2	26	13		46	23		67	50		82	103		
	3	30	15		56	28		62	47		84	105		
	4	x2			x2			x3			x5			
Yes	5	20	10		42	21		70	53		81	101		
	6	14	7		40	20		65	49		76	95		
	7	19	10		38	19		60	45		82	103		
	8													
	9	x2			x2			x3			x5			
dc312	10	19	10		32	16		56	42		72	90		
	11	24	12		30	15		52	39		69	86		
	12	23	12		35	18		50	37		70	88		
	13													
	14	x2			x2			x3			x5			
Basal	15	22	11		48	24		71	53		80	100		
	16	24	12		52	26		62	47		81	101		
	17	24	12		50	25		60	45		78	98		
	18													
	19	x2			x2			x3			x5			
V3	20	20	10		40	20		51	38		66	83		
	21	15	8		42	21		55	41		62	78		
	22	19	10		44	22		52	39		68	85		
	23	x2			x2			x3			x5			
d-F	24	19	10		30	10		38	29		57	71		
	25	17	9		20	10		48	30		55	69		
	26	20	10		24	12		39	29		58	73		
	27													
	28	x1			x1			x2			x3			
	29	17	4		18	5		22	11		32	24		
V-F	30	10	3		19	5		27	14		39	29		
	31	9	2		19	5		24	12		40	30		

EFFICIENCY LINE 22-206

H460

	Day 1		Day 3		Day 5		Day 7	
			x3		x5		x10	
Control	25	19	52	39	70	88	98	245
x3	29	22	56	42	75	94	100	250
	26	20	50	38	72	90	92	230
7m	x3		x3		x3		x5	
	18	14	21	16	28	21	40	50
	17	13	19	14	30	23	38	48
	10	8	22	17	27	20	42	53
dl312	x3		x3		x5		x10	
	30	23	54	41	72	90	96	240
	27	20	44	33	68	85	98	245
	28	21	50	38	74	93	101	252
B-Hal	x3		x3		x5		x10	
	21	16	49	37	62	78	82	208
	27	20	47	35	68	85	90	225
	26	20	44	33	68	85	89	223
x3	x3		x3		x5		x10	
	30	23	52	39	71	89	95	238
	27	20	41	31	70	88	97	242
	25	19	49	37	68	85	99	248
1-F	x3		x3		x3		x5	
	15	11	20	15	29	22	38	48
	18	14	20	15	29	22	40	50
	16	12	18	14	30	23	38	48
y-F	x1		x1		x2		x2	
	7	2	7	2	15	8	20	10
	8	2	10	3	17	9	20	10
	6	2	9	2	15	8	24	12

H1299

	Day 1		Day 3		Day 5		Day 7		
	x2		x2		x3		x3		
Control	25	13	41	24	60	45	80	60	
2	30	15	42	21	62	47	88	66	
3	26	13	44	22	63	47	91	68	
4	x2		x2		x3		x3		
5	30	15	34	17	58	44	67	50	
6	23	12	38	19	56	42	70	53	
7	24	12	40	20	56	42	70	53	
8									
9	x2		x2		x3		x3		
dl312	20	10	40	20	62	47	89	67	
11	24	12	41	21	60	45	84	63	
12	20	10	40	20	60	45	86	65	
13									
14	x2		x2		x3		x3		
B-sal	23	12	41	21	59	44	86	65	
16	20	10	39	20	60	45	90	68	
17	24	12	36	18	64	48	88	66	
18									
V-3	x2		x2		x3		x3		
20	10	5	11	6	20	15	30	23	
21	15	8	19	10	22	17	36	27	
22	17	9	19	10	24	18	39	29	
23									
24	x2		x2		x3		x3		
d-F	20	10	32	16	55	41	72	54	
26	23	12	42	21	57	43	74	56	
27	25	13	36	18	55	41	70	53	
28	x2		x1		x2		x2		
29	9	2	10	3	20	10	30	15	
V-F	8	2	12	3	20	10	27	14	
31	13	3	16	4	24	12	29	15	

EFFICIENCY LIFE-22-206

AS49

	Day 1		Day 3		Day 5		Day 7		9
Central	x2		x3		x5		x5		
2	27	14	38	29	66	82	89	111	
3	30	15	42	32	60	75	90	113	
4	30	15	40	30	63	79	92	115	
5	x2		x3		x5		x5		
7	17	9	25	19	35	44	51	64	
7	19	10	27	20	36	45	52	65	
8	19	10	20	15	30	38	55	69	
9									
dl312	x2		x3		x5		x5		
11	27	14	38	29	60	75	80	100	
12	26	13	44	33	62	78	88	110	
13	30	15	41	31	64	80	90	113	
14									
Bagal	x2		x3		x5		x5		
16	24	12	41	31	58	73	90	113	
17	28	14	38	29	63	79	87	109	
18	25	13	40	30	60	75	81	101	
19									
V3	x2		x3		x5		x5		
21	28	14	40	30	62	78	90	113	
22	26	13	40	30	62	78	91	114	
23	24	12	39	29	60	75	90	113	
24									
d-F	x2		x3		x5		x5		
26	18	8	28	21	34	43	54	68	
27	17	9	30	23	37	46	52	65	
28	20	10	25	19	33	41	54	68	
29	x1		x1		x2		x3		
V-F	10	3	10	3	14	7	19	14	
31	8	2	12	3	16	8	20	15	
	8	2	9	2	13	7	22	17	

H3225

	Day 1		Day 3		Day 5		Day 7		
Control	x2		x3		x3		x5		
2	29	15	38	29	66	50	80	100	
3	23	12	40	30	59	44	81	101	
4	24	12	44	33	62	47	84	105	
7er	x2		x3		x3		x5		
5	24	12	33	25	50	38	77	96	
6	20	10	34	26	57	43	76	95	
7	20	10	30	23	54	41	72	90	
8									
9									
12312	x2		x3		x3		x5		
10	21	11	40	30	61	46	80	100	
11	24	12	41	31	63	47	80	100	
12	26	13	35	36	60	45	82	102	
13									
14									
B gal	x2		x2		x3		x5		
15	20	10	36	27	62	47	79	99	
16	20	10	37	28	58	44	78	98	
17	24	12	39	29	56	42	69	86	
18									
19									
x3	x2		x3		x3		x5		
20	20	10	41	31	62	47	82	103	
21	18	9	42	32	60	45	71	89	
22	23	12	40	30	60	45	70	88	
23									
24									
d-7	x2		x3		x3		x5		
25	18	9	30	23	48	36	64	80	
26	20	10	34	26	50	38	79	99	
27	20	10	37	28	46	35	70	88	
28									
29	x2		x2		x2		x2		
x-F	16	8	20	10	29	15	40	20	
30	18	9	20	10	30	15	39	20	
31	18	9	27	14	24	12	41	21	

			Day 1	sd			
Con-NHB	15	13	15	14.33333	0.942809	25	23
FEN	10	7	10	9	1.414214	21	20
dl 312	10	12	12	11.33333	0.942809	16	15
Lac Z	11	12	12	11.66667	0.471405	24	26
Adp53-1	10	8	10	9.333333	0.942809	20	21
dl- FEN	10	9	10	9.666667	0.471405	10	10
p53-FEN	4	3	2	3	0.816497	5	5

			Day 1	sd			
Con-H460	19	22	20	20.33333	1.247219	39	42
FEN	14	13	8	11.66667	2.624669	16	14
dl 312	23	20	21	21.33333	1.247219	41	33
Lac Z	16	20	20	18.66667	1.885618	37	35
Adp53-1	23	20	19	20.66667	1.699673	39	31
dl- FEN	11	14	12	12.33333	1.247219	15	15
p53-FEN	2	2	2	2	0	2	3

			Day 1	sd			
Con- A549	14	15	15	14.66667	0.471405	29	32
FEN	9	10	10	9.666667	0.471405	19	20
dl 312	14	13	15	14	0.816497	29	33
Lac Z	12	14	13	13	0.816497	31	29
Adp53-1	14	13	12	13	0.816497	30	30
dl- FEN	8	9	10	9	0.816497	21	23
p53-FEN	3	2	2	2.333333	0.471405	3	3

			Day 1	sd			
Con-H322	15	12	12	13	1.414214	29	30
FEN	12	10	10	10.66667	0.942809	25	26
dl 312	11	12	13	12	0.816497	30	31
Lac Z	10	10	12	10.66667	0.942809	27	28
Adp53-1	10	9	12	10.33333	1.247219	31	32
dl- FEN	9	10	10	9.666667	0.471405	23	26
p53-FEN	8	9	9	8.666667	0.471405	10	10

			Day 1	sd			
Con-H129	13	15	13	13.66667	0.942809	24	21
FEN	15	12	12	13	1.414214	17	19
dl 312	10	12	10	10.66667	0.942809	20	21
Lac Z	12	10	12	11.33333	0.942809	21	20
Adp53-1	5	8	9	7.333333	1.699673	6	10
dl- FEN	10	12	13	11.66667	1.247219	16	21
p53-FEN	2	2	3	2.333333	0.471405	3	3

	Day 3	sd
28	25.33333	2.054805
19	20	0.816497
18	16.33333	1.247219
25	25	0.816497
22	21	0.816497
12	10.66667	0.942809
5	5	0

53	50
53	49
42	39
53	47
38	41
29	30
11	14

	Day 5	sd
47	50	2.44949
45	49	3.265986
37	39.33333	2.054805
45	48.33333	3.399346
39	39.33333	1.247219
29	29.33333	0.471405
12	12.33333	1.247219

	Day 3	sd
38	39.66667	1.699673
17	15.66667	1.247219
38	37.33333	3.299832
33	35	1.632993
37	35.66667	3.399346
14	14.66667	0.471405
2	2.333333	0.471405

88	94
21	23
90	85
78	85
89	88
22	22
8	9

	Day 5	sd
90	90.66667	2.494438
20	21.33333	1.247219
93	89.33333	3.299832
85	82.66667	3.299832
85	87.33333	1.699673
23	22.33333	0.471405
8	8.333333	0.471405

	Day 3	sd
30	30.33333	1.247219
15	18	2.160247
31	31	1.632993
30	30	0.816497
29	29.66667	0.471405
19	21	1.632993
2	2.666667	0.471405

82	75
44	45
75	78
73	79
78	78
43	46
7	8

	Day 5	sd
79	78.66667	2.867442
38	42.33333	3.091206
80	77.66667	2.054805
75	75.66667	2.494438
75	77	1.414214
41	43.33333	2.054805
7	7.333333	0.471405

	Day 3	sd
33	30.66667	1.699673
23	24.66667	1.247219
26	29	2.160247
29	28	0.816497
33	32	0.816497
28	25.66667	2.054805
14	11.33333	1.885618

50	44
38	43
46	47
47	44
47	45
36	38
15	15

	Day 5	sd
47	47	2.44949
41	40.66667	2.054805
45	46	0.816497
42	44.33333	2.054805
45	45.66667	0.942809
35	36.33333	1.247219
12	14	1.414214

	Day 3	sd
22	22.33333	1.247219
20	18.66667	1.247219
20	20.33333	0.471405
18	19.66667	1.247219
10	8.666667	1.885618
18	18.33333	2.054805
4	3.333333	0.471405

45	47
44	42
47	45
44	45
15	17
41	43
10	10

	Day 5	sd
47	46.33333	0.942809
42	42.66667	0.942809
45	45.66667	0.942809
48	45.66667	1.699673
18	16.66667	1.247219
41	41.66667	0.942809
12	10.66667	0.942809

		Day 7	sd
99	103	105	102.3333 2.494438
101	95	103	99.66667 3.399346
90	86	88	88 1.632993
100	101	98	99.66667 1.247219
83	78	85	82 2.94392
71	69	73	71 1.632993
24	29	30	27.66667 2.624669

		Day 7	sd
245	250	230	241.6667 8.498366
50	48	53	50.33333 2.054805
240	245	252	245.6667 4.921608
205	225	223	217.6667 8.993825
238	242	248	242.6667 4.109609
48	50	48	48.66667 0.942809
10	10	12	10.66667 0.942809

		Day 7	sd
111	113	115	113 1.632993
64	65	69	66 2.160247
100	110	113	107.6667 5.557777
113	109	101	107.6667 4.988877
113	114	113	113.3333 0.471405
68	65	68	67 1.414214
14	15	17	15.33333 1.247219

		Day 7	sd
100	101	105	102 2.160247
96	95	90	93.66667 2.624669
100	100	102	100.6667 0.942809
99	98	86	94.33333 5.906682
103	89	88	93.33333 6.847546
80	99	88	89 7.788881
20	20	21	20.33333 0.471405

		Day 7	sd
60	66	68	64.66667 3.399346
50	53	53	52 1.414214
67	63	65	65 1.632993
65	68	66	66.33333 1.247219
23	27	29	26.33333 2.494438
54	56	53	54.33333 1.247219
15	14	15	14.66667 0.471405

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